VOLUME 3 NUMBER 8

NUTRITION REVIEWS

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Published Monthly by

THE NUTRITION FOUNDATION, INC.

CHRYSLER BUILDING NEW YORK, N. Y.

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SEP 19 1945 ©CIB 892017

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NUTRITION REVIEWS

VOL. 3 AUGUST, 1945 No. 8

NUTRITIONAL CONDITIONS IN HOLLAND

Holland was overrun by Germany the week of May 10, 1940, and for the following five years a deliberate policy of starving the Dutch was pursued by the conquerors. This was a particularly trying experience for the Dutch since Holland not only maintained a large dairy industry and raised an abundance of grains and vegetables, but also had stores of sugar, grains, and vegetable oils to last for an estimated period of five years, the latter having also been confiscated.

In the fall of 1944 advancing Allied armies liberated southern Holland, but the country north of the great rivers and the cities of western Holland remained in German hands. At that time the food situation became even more acute due to the national railway strike. This strike, requested by the Allied Command, was faithfully and completely carried out by the Dutch, without a single train moving to bring food supplies to the large cities. The country became virtually depleted not only of foodstuffs but also of heat, coal, electricity, and gas. Throughout the winter of 1944–1945 the average caloric intake for adults in many cities of western or "occupied" Holland was estimated at 1200 to 1400 and in March and April of 1945 at 800 to 1000 calories. The protein supply was almost limited to that furnished by potatoes, coarse bread, and a few sugar beets; many people were dying of simple starvation. However, some cities, as for example Utrecht and Alkmaar were not so severely deprived.

With the complete liberation of the country approaching in the spring of 1945 the Allied Command and the Dutch prepared to give quick aid. Fifty special Red Cross Feeding Teams, each consisting of a physician and 15 Red Cross workers, were equipped with adequate motor transport and supplies of skim milk powder, sugar, gruel, and a casein hydrolysate preparation. Before deployment of these teams to the areas of Holland, it seemed necessary to assess rapidly the nutritional status of the population and to ascertain what food supplies were immediately available. Two "spearhead" nutrition teams were organized, one American and one Canadian, both augmented by Dutch personnel and by American and English nutrition consultants.

These two survey teams moved into Utrecht on May 7 along with the army of liberation and in the brief period of one week made an initial survey of the principal areas of western Holland. Recommendations for feeding programs were submitted to the Allied Command and to the Dutch public health and military officials. The usual procedure in surveying an area consisted first of a visit to the burgomaster and then conferences with the city health officials, leading physicians, and food ration authorities. Representative hospitals and housing institutions were inspected, and a "street clinic" was held in an area representative of the poor class. At such "clinics" approximately 150 people taken at random, but selected for age groups, were examined for signs of nutritional deficiency. Dietary histories were taken from 20 to 25 of the adults. Special home visits were made to individuals reported as severely ill and requiring emergency feeding. The results were discussed by the survey team and a report prepared before moving to another city. In this way Utrecht, Amsterdam, Rotterdam, The Hague, Delft, Leiden, Hilversum, Dordrecht, Amersfoort, Haarlem, Alkmaar, and various rural areas were surveyed.

Clinical evidence of real starvation was abundant in all urban areas, the most

pronounced findings being weight loss, pallor, cachexia, and edema. Frequent cases of "hunger osteopathy" or "Milkman's Syndrome" were also observed. Classic vitamin deficiency syndromes were rarely seen although folliculosis, cheilosis, glossitis, and papillary atrophy were frequent. Weakness, fatigue, diarrhea, muscle pains, and paresthesias were common complaints. Average caloric intakes were found to range from 500 to 1000 calories per day. Along with starvation, certain diseases had increased considerably. Tuberculosis morbidity had increased four to five times, and enteritis and a nonspecific toxic dysentery, which before the war were rare in Holland, were now present in 15 to 20 per cent of the population. Peptic ulcer and hernia had greatly increased. Interestingly enough, heart disease, hypertension, and obesity had greatly diminished. Lack of soap and hot water led to miserable conditions with the common insect infestations. A brief description of the specific findings in Rotterdam might best portray the nutritional findings.

Rotterdam, the chief port of Holland and the second largest city, has a population of 600,000. The weight loss in adults had averaged 25 pounds and the condition of infants was poor due to lack of milk. At least half of the children from 1 to 12 years of age were more than 10 per cent below the average weight and height for Dutch children. During four months of the spring of 1945 an average of 1100 people per day had applied for extra food because of nutritional edema. On May 9 it was estimated that there were 40,000 cases of hunger edema in Rotterdam alone. The death rate for the first three months of 1945 was 2300 as compared with the prewar rate for the same period of 900; many of these deaths appeared due to simple starvation. The results in per cent of the "street clinic" in Rotterdam were: general appearance, normal 2, fair 36, poor 52, serious 10; pallor, 65; cheilosis, 40; follicular hyperkeratosis, 38; edema, 18.

"Hunger hospitals" had been organized in Rotterdam to care for the most incapacitated individuals. Most patients were admitted with massive edema which cleared fairly quickly on bed rest and extra food, leaving them emaciated and weak. Of three such "hunger hospitals" visited one had 75 cases of severe starvation, another 20, and a third 300. Of 40 patients picked at random, there was an average weight loss of 55 pounds, anemia was severe in all, open sores were present in 10, and massive edema in 28.

The children of Rotterdam were in unusually poor condition. Of 28 children, who were carefully examined, some 90 per cent showed pallor, folliculosis, and gingivitis, and 50 per cent showed cheilosis and glossitis. Six of these children were so weak and emaciated they could not stand and they lay on the floor with knees drawn up, ghastly pale, and listless. In the opinion of the leading pediatricians the most severe deficiencies in children were calories, protein, fat, vitamin A, calcium, and iron. Two weeks after the survey, emergency "hunger hospitals" were established for children and one thousand beds are now available for this purpose. It is strange, indeed, to be in a ward with a hundred young children and hear scarcely a sound for they all lie quietly in bed, completely fatigued.

Careful dietary histories taken from housewives in twenty-six homes of the poor class yielded the following estimates of daily food intakes (figures in grams): bread, 23; thin soup, 211; potatoes, 97; cauliflower, 75; milk, 20; sugar, 75; cheese, 2; peas, 4; and oats, 10. This dietary furnished approximately 630 calories.

The city of Hilversum with a population of 80,000 showed general conditions similar to those of Rotterdam. Here a Central Kitchen had served approximately 30,000 people a day when food was available. Die-

tary histories in this city gave the following daily food intakes (figures in grams); bread, 114; potatoes, 205; cauliflower, 210; porridge, 90; clear soup, 175; oil, 3; milk, 33; and meat 3. This represented 740 calories with 36 g. of protein and 7 g. of fat.

Delft with a normal population of 56,000 had received some 3000 evacuees from The Hague and Rotterdam. Cases of hunger edema were common and the city health department estimated that approximately 100 deaths had occurred this year from uncomplicated starvation. The dietary was similar to that of the other cities, yielding approximately 785 calories, with 33 g. of protein and 5 g. of fat. The "Central Kitchen," operated by volunteer organizations, was feeding 34,000 people one-half liter of vegetable soup each day.

On the basis of these studies a conservative estimate of the number of persons with hunger edema or cachexia, not including infants, in the principal areas of western Holland during the second week of May, 1945 was as follows: Amsterdam 30,000; Rotterdam 40,000; The Hague 17,000; Haarlem 15,000; Utrecht 3000; Delft 2000; Dordrecht 1000; Hilversum 1000; Leiden 1000; several small communities 15,000; a total of 125,000.

These one day "spearhead surveys" of western Holland were accomplished in the first week following liberation. The survey teams then began a more thorough study of a few of the principal areas and augmented the studies with total protein and hemoglobin estimations. These studies were planned to include an adequate representation of the poor, middle, and upper classes and have completely supported the findings of the previous one day surveys. The evidence of starvation is not limited to the poor populations though some of the findings are more marked in this group. Weight loss, pallor, and the complaints of diarrhea, fatigue, and weakness are equally prevalent in the people of the middle and upper class districts. The arrival from England of a mobile laboratory staffed by members of the Oxford Nutrition group permitted many more laboratory studies to be made. The results of all of the various nutritional studies now being made in Holland, and those that were made by Dutch scientists during the war, will soon be put together in one report which it is hoped will be published in 1946.

It is thus apparent that starvation was a real and serious problem in occupied Holland and reports to the contrary were not based on factual evidence. It is difficult to state which deficiency presented the most serious problem, for the deficiency was one of food, not of one or two specific nutrients. On the basis of clinical findings, calories (particularly fat), protein, iron, vitamin A, riboflavin, and in infants, calcium, seemed the most serious deficiencies. As of this writing (June 1, 1945), the food situation has already improved greatly, and it undoubtedly will continue to do so. Daily caloric intakes are now estimated at 1500 calories and the protein quantity and quality have improved although there are still serious deficiencies of fat. It will take much food and time to repair the damage inflicted by "organized starvation" in Holland.

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THE METHYLATION OF NICOTINAMIDE

The designation F_2 has been given to a substance excreted in the urine which possesses a bluish fluorescence in ultraviolet light when treated with alkali and butanol. Najjar and Holt (*Science* **93**, *20 (1941)*) showed that this substance is absent in the urine in cases of nicotinic acid deficiency and that its quantity varies directly

with the intake of nicotinic acid or nicotinamide. Chemical studies by various workers (Huff and Perlzweig, *Ibid.* **97,** *538* (*1943*); Najjar, Scott, and Holt, *Ibid.* **97,** *537* (*1943*)) have shown that this compound is a methylated nicotinamide, N^1-methylnicotinamide (F_2). A test has been devised for the diagnosis of nicotinic acid deficiency based on the measurement of this substance.

Najjar now proposes that the measurement of this substance may provide a simple means for the study of methylation in the nondeficient individual. Perlzweig, Bernheim, and Bernheim (*J. Biol. Chem.* **150,** *401* (*1943*)) showed that nicotinamide is methylated *in vitro* by liver slices but not by kidney or muscle tissue. Najjar, Hall, and Deal (*Bull. Johns Hopkins Hosp.* **76,** *83* (*1945*)) have studied methylation in the kidney *in vivo* in a dog. The right kidney was severed and served as a control. The left kidney was shelled out of its capsule and brought out of the abdominal cavity, leaving its arterial supply and venous drainage intact. The ureter was dissected out, severed at its junction with the bladder, and allowed to drain into a test tube. The renal vein was clamped and a 25 ml. control sample of blood was obtained from the vein on the renal side of the clamp. Fifty milligrams of nicotinamide were then injected into the renal artery during a period of about two minutes while blood was simultaneously being withdrawn from the vein in order to establish a continuous blood flow, as well as obtain blood samples. The kidney finally was completely severed and weighed slices used for assay. Study of methylation in the liver *in vivo* was done by detaching it from the surrounding organs to eliminate any aberrant blood supply, removing a piece of liver tissue and a sample of blood from the hepatic vein as control specimens, and clamping the hepatic artery and portal vein. Fifty milligrams nicotinamide were immediately injected into the portal vein on the hepatic side of the clamp, while samples of blood were being withdrawn from the hepatic vein. By this means it was assured that the nicotinamide injected could not be methylated elsewhere and returned as such to the liver. A piece of liver tissue was removed during the injection which lasted about three minutes and three other pieces were cut out at approximately one minute intervals after the injection. Samples of the tissue obtained were thoroughly ground and extracted with acetate buffer over a steam bath for twenty minutes. All extracts were assayed for N^1-methylnicotinamide by the method of Najjar (*Bull. Johns Hopkins Hosp.* **74,** *392* (*1944*)).

The results showed that the intact kidney was incapable of methylating nicotinamide. There was no demonstrable increase of the methylated compound either in the blood or in the renal tissue after infusion with nicotinamide. Even the urine collected from the infused kidney showed no increase in F_2. On the other hand the F_2 content of the liver tissue rose promptly during the injection from a value of 0.90 microgram per gram in control specimens to 3.8 micrograms per gram and higher in specimens obtained after nicotinamide had been infused. Measurements on the blood taken from the hepatic vein showed a substantial increase in the quantity of F_2 following infusion with nicotinamide. The data indicated that the total amount of nicotinamide that was methylated by the liver was nearly 3 per cent of the injected dose, an amount which is considerable in view of the short time allowed for the experiment and the fact that nicotinamide passed only once through the liver tissue. When to this is added the quantity which escaped through the hepatic vein as shown by the rise in the blood level during the infusion, the total amount methylated and excreted from the liver in the experimental animal appeared to account for what is found by measurements in the urine in the normal intact dog.

Najjar concludes that the evidence is certainly strongly suggestive that the liver is the most important organ methylating

nicotinamide, if not the only one. He reports preliminary observations on the use of this procedure as a means of testing liver function. The urinary output of methylated nicotinamide during a four-hour period following a load test of either 50 mg. nicotinamide by mouth or 20 mg. injected intravenously was measured. Results in 15 patients with presumably no liver disease were compared with 14 suffering from nephrosis, diabetes mellitus, catarrhal jaundice, or glycogen disease, and revealed a comparatively low proportion of methylated compound in the urine of the latter. The use of this procedure as a test for the methylating function of the liver would presuppose the availability in the patient before the test of optimal quantities of nicotinamide and perhaps also of substances like methionine, choline, and methyltestosterone which must supply the methyl radicle. With these and perhaps other limitations which further studies may reveal, the method proposed may prove to be a useful test of another of the many functions of the liver. As the authors point out, such a hepatic function test has the particular advantage that the test substance is a vitamin and is not apt to induce other than physiologic responses from the body. The methylated product is likewise physiologic, since it is found normally in tissues and apparently possesses biologic properties.

VITAMIN A DEFICIENCY AND INFECTION

It has been suspected for a long time that animals and human beings which are deficient in vitamin A are susceptible to infection. Impressive amounts of data in support of this conclusion have been accumulated, both of the nature of clinical observations and in the field of carefully controlled animal experimentation. The further suggestion that the maintenance of resistance to infection is a more or less specific function of vitamin A gained considerable support for a time. Even today it must be regarded as a controversial subject, although a great deal of evidence which fails to support this point of view has been presented. It should be kept in mind in this connection that attempts to increase resistance to infection by administering amounts of vitamin A in excess of normal requirements have proved unsuccessful.

It was largely as a result of the work of Green and Mellanby (*Brit. Med. J.* **2,** *691 (1928)*) that the term "anti-infective" was applied to vitamin A. They suggested this term on the basis of their own results and those of other investigators. In their study, 91 of 93 rats given diets deficient in vitamin A, but otherwise adequate, developed multiple infective lesions and died, while of several hundred rats deficient in vitamin D only 2 cases of gross infection were found. As a probable explanation, Green and Mellanby suggested that the epithelial changes known to occur in vitamin A deficient animals might have lowered the barrier to bacterial penetration, although they recognized the further possibility that an impairment of other processes involved in resistance to infection might be contributory. It was soon shown by other investigators that the difference between animals receiving adequate and inadequate amounts of vitamin A could be demonstrated even if the infective organism were introduced intraperitoneally. Attempts to demonstrate an increased permeability of epithelial tissue damaged by lack of vitamin A were unsuccessful, also. As a consequence of these experimental findings, many observers concluded that vitamin A functions as an anti-infective agent through its influence on general body resistance.

Kligler, Guggenheim, and Henig (*J. Hygiene* **44,** *61 (1945)*) proposed to answer the

question as to the degree of avitaminosis A necessary to lower the resistance to infection. Rats and mice served as the experimental animals and S. typhi-murium as the infective agent. One week after weaning these animals were given a diet consisting of alcohol-extracted casein, rice flour, olive oil, yeast, salt mixture, and vitamin D. Control animals received the same diet and were given a supplement of vitamin A in olive oil. At the beginning of the experiment, the livers of the rats and mice contained small amounts of vitamin A, as demonstrated by analyses made on representative animals. After one week or less on the deficient diet, these reserves disappeared. Normal growth continued for approximately one week longer, then slackened and stopped, followed by loss of weight. The deficient rats showed keratomalacia and xerophthalmia in the sixth or seventh week of the experiment at a time when the weight curves had started down; at no time did the mice develop these signs. The deficient animals were divided into groups on the basis of the severity of the deficiency, as indicated by weight behavior. Animals which were growing at a reduced rate and which were believed to have no vitamin A reserve in the liver were considered hypovitaminotic; those which were no longer growing or were losing weight were considered to be avitaminotic. Together with the controls which received vitamin A they were then inoculated *per os* with S. typhi-murium. The strain used was virulent for mice and moderately so for rats. The dosage was one which had been shown to give a mild to a moderate infection in normal animals.

There were striking differences in the reaction of normal and avitaminotic mice and rats to the infective organism. The infection proceeded more rapidly in the avitaminotic animals, the total fatality was higher and there was a higher incidence of positive cultures from the mesenteric glands, liver, and spleen. On the other hand, no difference was discernible between the hypovitaminotic animals and the controls. It appeared therefore that the susceptibility to infection developed in vitamin A deficient rats only after the deficiency became severe, that is after the animals had begun to eat less and to decline in weight.

This observation raised a question as to the role which inanition might play in the susceptibility to infection. Accordingly, a paired feeding experiment with rats was carried out. One group received the vitamin A deficient diet, the second group received vitamin A and were fed ad libitum, while the third group received vitamin A with the food intake limited to that of the deficient group. The starved rats receiving vitamin A fared no better than the deficient animals; the incidence and distribution of the infection was the same. The well fed group on the contrary were protected to a large extent against the infection. Kligler *et al.* concluded that in vitamin A deficient animals it is the starvation rather than the vitamin deficiency which is responsible for the lowered resistance.

These results illustrate the importance of considering the food intake in experiments of this type. Additional and corroborative data must be accumulated, of course, before we can accept as a general rule that the "anti-infective" effect of vitamin A is merely an effect on the appetite, but there can be little doubt that inanition is a complicating factor which should be controlled. In view of the widespread popular, and to some extent professional, belief in the efficacy of vitamin A as an "anti-infective" agent, it is to be hoped that these results will stimulate further work along these lines.

EFFECTS OF VITAMINS IN DIABETES

It has been known since the latter part of the nineteenth century that yeast may benefit the diabetic. The exact nature of the substance or substances present in yeast which are responsible for this effect has been the subject of much speculation and many researches. It was once postulated that there existed in yeast and other plant materials an insulin-like hormone, designated as "glucokinin." It was even seriously considered by other investigators that insulin and "vitamin B" might be chemically identical. It has now been demonstrated that the beneficial effect of yeast in a diabetic dog can be duplicated by a mixture of seven of its known constituent vitamins (or vitamin-like substances). The mechanism whereby the effect is produced, however, remains rather obscure.

In 1937, Martin (*Z. f. physiol. Chem.* **248,** *242 (1937)*) showed that the insulin requirement of depancreatized dogs increased steadily during the ingestion of a diet low in vitamins. The diet consisted of ground horse meat, thoroughly autoclaved at 110°C., sucrose, and bone-ash. Sufficient insulin was given to control the diabetes. During the first four weeks on this regimen, there was a mild glycosuria and a slightly elevated fasting blood sugar. The clinical condition of the dogs was satisfactory and they gained a little in weight. After five to seven weeks, however, the level of sugar in the blood and urine rose. If no change in the regimen was made, these levels became higher and the animals died. The administration of increasing amounts of insulin relieved the condition only temporarily. Finally a stage was reached where the diabetes was no longer controllable by insulin. Despite the administration of as much as 160 units daily, there was a large urinary output of sugar (125 to 165 g. daily in one experiment). The administration of a soybean preparation rich in choline had no beneficial effect. One animal which was receiving 60 units of insulin and excreting approximately 60 g. of sugar daily was treated with a combination of vitamin concentrates which contained vitamins C, A, and D, and the vitamin B-complex. Relief of the condition was so rapid that on the first day that these concentrates were given it was necessary to administer 35 g. of sugar to prevent insulin shock. This animal was later successfully treated with a mixture of crystalline thiamine and crystalline riboflavin. Thiamine alone appeared to be ineffective, and riboflavin alone was not adequately tested. The other 2 animals which were used in the experiments failed to respond to yeast or to vitamin concentrates and succumbed.

Dienst (*Deutsche med. Wchnschr.* **65,** *710 (1939)*) tested the clinical effect of a vitamin preparation on 6 diabetic patients. These patients were given diets which were believed to be completely adequate and of known carbohydrate, fat, and protein content. They showed no signs of any vitamin deficiency. After a control period of several weeks, the vitamin concentrate was added to their regular diet. This preparation contained known amounts of vitamin C and thiamine and unknown amounts of other vitamins, particularly of the B-complex. The carbohydrate tolerance was improved in all 6 patients. The daily insulin requirement was reduced by approximately 20 units and in some cases hypoglycemic reactions were noted. Fluctuations in the blood sugar level were reduced also. Dienst attributed these effects to vitamin C and thiamine and suggested that the addition to the diet of added amounts of other members of the B-complex might be of value in permitting the added thiamine to exert its optimal effect. He interpreted his results as indicating that the vitamin requirements of the diabetic patient, particularly for thiamine, are higher than those of normal individuals.

Gaebler and Ciszewski (*Endocrinology*

36, *227 (1945)*) reinvestigated the effect of yeast in the depancreatized dog. In one series of experiments, they also successfully substituted seven known ingredients for the yeast. Their animals, following pancreatectomy, were given a diet consisting of casein, cracker meal, corn oil, salt mixture, and yeast with supplements of haliver oil and pancreatin. This diet contained approximately 35 per cent of protein, 25 per cent of fat, and 30 per cent of carbohydrate. The insulin requirement of each animal was determined by long preliminary observations and was supplied in two forms, free and in combination with protamine. In 2 of 3 animals withdrawal of yeast with the insulin dosage remaining constant was followed by progressive glycosuria, loss of weight, marked rise of urinary nitrogen, and a negative nitrogen balance. The glycosuria was accompanied by an increase in and a prolongation of the alimentary hyperglycemia that followed meals. The daily output of glucose reached a level of 50 to 70 g. which approximately equaled the amount of carbohydrate present as such in the diet. When yeast feeding was resumed, the glycosuria was abolished and nitrogen equilibrium was restored. In one of these 2 animals the glycosuria was controlled, for fifty-two days, by increasing the insulin dosage by 50 per cent. This animal then began to refuse the diet and the feeding of yeast was resumed. In the third animal withdrawal of yeast from the diet produced neither glycosuria nor a rise of the blood sugar curve.

One animal was used in a study of the substitution of known vitamins for yeast. It was found that the effects of yeast could be duplicated by feeding seven of its known constituents: thiamine, riboflavin, niacin, inositol, pyridoxine, pantothenic acid, and p-aminobenzoic acid. The combination of three of these, thiamine, riboflavin, and niacin, prevented loss of nitrogen almost completely but only delayed the onset of glycosuria. Evidence was obtained which suggested that inositol was one, but not the only factor active in preventing glycosuria.

The beneficial effect of yeast in cases of human diabetes and in depancreatized dogs is of unquestioned interest, and it appears that a beginning has been made in the identification of the active constituents. The data which have been presented from different laboratories are somewhat contradictory, however, and in any event are not sufficiently extensive to clarify the situation. Further work is needed both to identify the vitamins involved and also to explain the mechanism whereby their effect becomes operative.

RELATION OF REPEATED BLEEDINGS TO CIRRHOSIS OF THE LIVER

Holman (*J. Exp. Med.* **81,** *399 (1945)*) reports observations which suggest that repeated bleeding in dogs fed a relatively high fat diet results in cirrhosis of the liver, whereas neither diet nor repeated bleeding alone produces such changes in the liver. The dogs had been subjected to repeated removal of blood over a period that varied from one to three years. In these animals some 200 to 250 ml. or roughly 15 per cent of the total blood volume had been removed at intervals averaging about two times per month. These dogs had been fed a kennel diet that for a period of over a year consisted of beef bones with much adherent fat. Examination of the livers of 13 animals revealed unexpectedly that 3 showed advanced cirrhosis, 7 slight to moderate cirrhosis, and 2 marked fatty change without definite increase in portal connective tissue. In only one animal was the liver normal. The hepatic changes which were observed appeared to be identical with those described by Chaikoff, Eichorn, Connor, and Enten-

man (*Am. J. Path.* **19,** *9* (*1943*)), and by Graef, Negrin, and Page (*Ibid.* **20,** *823* (*1944*)).

In the cases of advanced cirrhosis the liver was grossly nodular although the nodular pattern was not uniform; areas of nodular hyperplasia were scattered between areas of atrophic fibrotic change. The livers of the animals showing moderate changes varied considerably in appearance, but fibrotic changes and moderate large droplet fatty changes were seen in all. In one instance central necrosis was observed. In several livers there was a definite increase in periportal connective tissue with slight to moderate bile duct proliferation and lymphocytic infiltration, as well as moderate large droplet fatty change in the hepatic cells. In the livers showing the least marked changes, moderate to marked large droplet fatty change in the hepatic cells was observed, but there was no definite increase in connective tissue or other change in the portal areas. In contrast to these findings, 4 dogs which had not been bled and which received relatively high fat diets similar to those in the 13 animals described, were found to show no cirrhosis or marked fatty changes in the liver.

A planned experiment with accurate records of diet and bleeding, and with adequate controls, supplemented by chemical analyses of blood and liver lipoids, will be necessary before these observations can be given much consideration. Nevertheless, they are of sufficient interest to note and record.

EVALUATION OF THE RELATIONSHIP OF URINARY F_2 TO NIACIN NUTRITION

It is of great importance to be able to detect a deficiency state in its larval stages rather than to wait until the structure of the superficial tissues of the body have been sufficiently disturbed to furnish diagnostic signs. A specific deficiency state develops typically in four stages: Stage one in which the dietary intake of the specific nutrient is inadequate; stage two in which the tissues become depleted; stage three in which metabolic defects appear; and stage four in which structural changes occur. In certain instances it has been possible to detect stage two by observing decreased concentrations of the particular nutrient in the urine. This is particularly feasible if the nutrient is excreted largely in unaltered form as, for example, in the case of ascorbic acid.

With niacin a more complicated situation exists, since this vitamin is excreted in at least five different forms in the urine; viz., niacin, niacinamide, nicotinuric acid, trigonelline, and N-methylnicotinamide or F_2. The problem is to determine whether the measurement of any or all of these compounds would be useful in the assessment of nutritional status. Of the five, F_2 is the most readily determined and has received considerable recent attention.

Najjar, Holt, and associates have carried out extensive studies of this substance and its usefulness in the diagnosis of human pellagra and canine blacktongue (*Science* **93,** *20* (*1941*); **97,** *537* (*1943*); *J. Clin. Invest.* **21,** *263* (*1942*); *Pa. Med. J.* **46,** *451* (*1943*); *Journal-Lancet* **63,** *366* (*1943*); *Federation Proceedings* **1,** *117* (*1942*); *Bull. Johns Hopkins Hosp.* **70,** *329* (*1942*); and *Proc. Soc. Exp. Biol. Med.* **44,** *386* (*1940*)). As niacin deficiency advances, the daily excretion of F_2 declines from its normal level to zero, and when pellagrins are vigorously treated with niacinamide the urinary F_2 increases. Najjar and Holt extended these observations to normal persons and reported that when F_2 is absent from the urine collected in the postabsorptive state the stores of niacin are low. F_2 promptly rises in normally fed persons following administration of nicotinamide. These findings have been corroborated by Coulson,

Ellinger, and Platt (*Biochem. J.* **36,** *xii* (*1942*)).

Investigators at the Harvard Fatigue Laboratory have undertaken the development of methods for rapid field testing of the biochemical and nutritional status of young men (Sargent, Robinson, and Johnson, *J. Clin. Invest.* **23,** *714* (*1944*)). In agreement with Najjar and Holt they found that urinary F_2 levels in healthy young men usually correlated with dietary and clinical evidence of their niacin stores, but a few exceptions occurred in men who were eating an adequate diet and, nevertheless, excreted no F_2. In a single subject who fasted for sixteen days the F_2 reached high levels. After test doses of niacinamide there was usually a rise in excretion of urinary F_2. However, there were certain subjects, known to be adequately supplied with dietary niacin, who had no increase in urinary F_2 following test doses. In addition to these extremes there was a wide variety of individual responses to niacin.

Mickelsen and Erickson (*Proc. Soc. Exp. Biol. Med.* **58,** *33* (*1945*)) have reported further evidence concerning the relation between dietary intake of niacin and F_2 excretion. Eight subjects were maintained for over five months on a controlled niacin intake. Four received 12 mg. niacin per day; the other 4 received 22 mg. per day. During the entire five months there was never any significant difference in the F_2 excretion of the two groups. At the end of this period the niacin intakes were changed from 12 to 0.1 mg. per day for the first 4 subjects and from 22 to 10 mg. per day for the others. During the ensuing month there still was no demonstrable difference in the F_2 excretion of the two groups, even though niacin was nearly eliminated from the diet of the first 4 subjects.

It would thus appear that although F_2 has some value as a measure of niacin intake, certain important problems need to be resolved before it can be used as a completely reliable index of the niacin status of the individual. Mickelsen and Erickson mentioned analytical difficulties. They used two different procedures and tested a third, each of which gave radically different results. It is conceivable that some of the present ambiguities in regard to the relationship between niacin and F_2 excretion will be resolved by improvements in analytical methods.

Niacin is apparently metabolized at varying rates along many different metabolic pathways. Sarett, Huff, and Perlzweig (*J. Nutrition* **23,** *23* (*1942*)) and Perlzweig, Bernheim, and Bernheim (*J. Biol. Chem.* **150,** *401* (*1943*)) have discussed the multiplicity and variability of intermediaries and end products of niacin metabolism, and the latter workers showed that aerobic methylation of nicotinamide by sliced rat liver is sometimes enhanced by methionine. It also appears that niacinamide is more completely converted to F_2 than is niacin itself. Therefore, one would anticipate relatively small increases in F_2 excretion in experiments, such as those of Mickelsen and Erickson, in which niacin rather than niacinamide is given as the supplement. Because of the unreliability of any single type of compound as a measure of total niacin metabolism, it would appear desirable to study all known related compounds in the urine in appraising the nutritional status and gauging the stores in the body. Such work is a complex laboratory procedure.

Opinion is at present divided as to the significance of F_2 excretion for the evaluation of niacin nutrition. The extensive studies of this problem which are being made at the present time should clarify this situation.

RIBOFLAVIN EXCRETION AND REQUIREMENT OF MAN

Extensive observations on the excretion of riboflavin have been made by Hagedorn, Kyhos, Germek, and Sevringhaus (*J. Nutrition* **29,** *179 (1945)*), using long term prison inmates who volunteered as experimental subjects. Twenty-four hour urine samples were collected in dark brown glass bottles with glacial acetic acid, chloroform, and toluene, transported to the laboratory and refrigerated under toluene. Riboflavin was assayed in each sample within three days by the microbiologic method. Evidence was obtained that riboflavin loss from the samples before assay did not occur to any significant extent. Single urine samples were obtained from 68 men in a preliminary study, and the riboflavin output for twenty-four hours varied from 0.05 to 2.4 mg.

It was not possible to measure the food intake of the individual subjects, but certain information was recorded. All of the subjects received a regular prison ration, in which the chief source of riboflavin was milk offered in amounts of from 9 to 10 cups weekly. Some men rejected the milk wholly or almost wholly, some men took the whole of the ration without additions, while still others took the whole ration and had additional sources of riboflavin in extra milk, liver, peanuts, or vitamin preparations. Among 43 individuals giving definite and reliable information about their food habits, which were believed to be of long standing, it was observed that 14 who drank less than 3 cups of milk weekly all excreted less than 0.2 mg.; 16 who took 9 to 10 cups weekly with no additions to the regular ration excreted 0.2 to 0.5 mg.; and 13 who had extra sources of riboflavin in addition to the regular ration excreted 0.5 to 2.4 mg. of riboflavin.

From this group of 43 subjects 29 were available for a prolonged study, and twenty-four hour urine samples were obtained from them at intervals for fifteen months. Sunday was chosen as the day of collection, and the menus for Saturday and Sunday were standard. There were 5 subjects classified in the first group described above, 16 in the second group, and 8 in the third group. For each subject, the average of his twenty-four excretion of riboflavin fell within those limits observed for his group and stated above.

Physical examinations were made of the 29 subjects, using a portable slit-lamp and examining only the eyes, nose, lips, tongue, and gums. Of the 5 men in the low intake group, who had been avoiding milk consumption for two or more years, one had grossly visible corneal injection and one had a questionable "cheilitis" at the lips. Among the 16 men taking the whole prison diet 14 showed corneal injection and 5 had "tongues with distinct furrows," but none showed cheilosis. Of the 8 men who ingested extra riboflavin, 4 had corneal lesions, 2 had furrowed tongues, and one showed evidence of cheilitis.

Some observations on the retention of riboflavin supplements were made, using over a period of three to six weeks supplements of milk, yeast tablets, or synthetic riboflavin. The rather scattered data obtained are difficult of precise interpretation, and the use made of some of them in an extrapolation procedure for calculating the riboflavin intake of some individuals appears to be unjustifiable. (*See* Snedecor, "Statistical Methods," *Sections 14.3 and 14.6, Collegiate Press, Inc., Ames, Iowa (1938).*) A test was also made of the use of one hour urine samples of fasting subjects, recommended by Holt (*Pa. Med. J.* **46,** *451 (1943)*), but the authors considered that the errors in measuring the very low riboflavin concentrations encountered were too great to permit such samples to be very useful.

In discussing their results as a whole Hagedorn, Kyhos, Germek, and Sevringhaus (*loc. cit.*) note that signs such as cheilosis, nasolabial skin changes, or chronic

lesions of the scleras were not correlated with low intake of riboflavin, such signs being indeed least common in the group with the lowest riboflavin intake. They therefore question the value of such signs as evidence of long continued riboflavin deficiency. Their evidence is an important item to add to much previously existing evidence suggesting that these signs are not specific for riboflavin deficiency (Dann and Darby, *Physiol. Rev.* **25,** *326 (1945)*). It is particularly important because the riboflavin intake of the subjects was known (though only approximately) for two years or more, and varied little for any one subject throughout this period. Thus the evaluation of riboflavin intake was not based on the recorded ingestion over a short period of only a few days or a week near the time of the physical examination.

The retention of riboflavin supplements varied widely without apparent reason, causing the authors to criticize tests based on the excretion of test doses ("saturation tests") as evidence of riboflavin deficiency. They conclude that satisfactory criteria of riboflavin deficiency in adults are still lacking, and as a corollary that there is still an urgent need for the presentation of evidence from physical examination or from biochemical studies which will be useful in the detection of such deficiency.

FUNCTIONAL VITAMIN FORMS IN HEART MUSCLE

It is now well recognized that several of the vitamins must assume a different chemical form in the tissues before their catalytic role in metabolism is possible. In the case of the B-vitamins, thiamine, niacin, and riboflavin, uniting with phosphate, is at least the first necessary step in the formation of the active coenzyme. The functional form of thiamine is commonly called cocarboxylase or diphosphothiamine, and that of niacin, coenzyme I. It is conceivable that in certain conditions the functional form of a vitamin may be lacking in spite of adequate amounts of the free vitamin.

In a previous review (*Nutrition Reviews* **3,** *89 (1945)*) the studies of Govier and Greig were discussed. These investigators have presented data which may be interpreted as indicating that in shock and in anoxia a loss of phosphate from cocarboxylase occurs and that shocked animals, although well supplied with thiamine, become in a sense thiamine-deficient since their thiamine is in the free form, useless to tissue metabolism. These workers postulated that both anemic anoxia and anoxic anoxia produce a tissue anaerobiosis which results in breakdown of cocarboxylase.

Carrying this work further, Govier (*Am. Heart J.* **29,** *384 (1945)*) reports on the effect of anoxic conditions on the content of cocarboxylase and coenzyme I in the heart muscle of the dog. The author infers in this work that the heart failure in such conditions may be due to loss of the functional forms of the vitamins. A prevention of the dissociation of the functional vitamin form was attempted by administration of the free form, reasoning perhaps that the chemical mass action principle would be operative under these conditions. A consideration of the details of carbohydrate metabolism led the author to administer succinate, a substance which can be oxidized by heart muscle with release of energy but without the need of cocarboxylase and coenzyme I.

Technically, anoxia of the heart was produced by tying the left anterior descending coronary artery. In some experiments nicotinamide, riboflavin, and succinate were given thirty minutes after the operation, in others one hour after the ligation. In all cases two hours after ligation of the vessel, the chest was reopened, the heart excised, and samples of the heart

muscle were removed from the area which had been deprived of blood, and from nearby areas of the heart muscle. These samples were quickly weighed, plunged into beakers of boiling water, and boiled for five minutes, after which the beakers were placed in a pan of ice water. After cooling, the samples were minced with scissors, homogenized, and the suspensions centrifuged. The supernatant fluid was analyzed for cocarboxylase by a manometric method and for coenzyme I by the method of Axelrod and Elvehjem (*J. Biol. Chem.* **131,** *77 (1939)*). The hearts of all the dogs were examined to make certain that actual occlusion of the artery had been accomplished. Electrocardiograms taken on a few of the animals after the operation showed what was regarded as unmistakable evidence of coronary occlusion.

In 6 experiments the coenzyme I content of the ischemic heart muscle was found to have been reduced an average of 76 per cent as compared with that found in the normal muscle. The values in the 6 experiments corresponded with one another to a remarkable degree. No consistent changes were found in the cocarboxylase content. In 5 instances in which 20 mg. of nicotinamide per kilogram of body weight were given intravenously one hour after the coronary artery had been ligated, a reduction of 58 per cent in the coenzyme content of the ischemic muscle was observed. This value was not significantly different from that found in the corresponding muscle of untreated animals. In another series consisting of 7 animals, nicotinamide was given before ligation of the coronary vessel. In these the average amount of reduction of coenzyme I in the ischemic muscle was only 32 per cent. This Govier regards as a significant difference as compared with the untreated animals. The administration of riboflavin together with nicotinamide to 4 dogs before coronary ligation, produced no significant improvement over the values obtained when nicotinamide alone was given.

Sodium succinate in amounts of 1 g. per kilogram of body weight was given intravenously to dogs before and after coronary ligation. The average breakdown of coenzyme I when this was given before ligation was 39 per cent; when injected after coronary inclusion 49 per cent, a probably insignificant difference. A study of the effect of succinate administration on cardiac function, rather than on coenzyme levels, might have been more significant to the problem.

Himwich, Goldfarb, and Nahum (*Am. J. Physiol.* **109,** *403 (1934)*) reported that the heart is unable to metabolize lactate after coronary occlusion. The finding that the quantity of coenzyme I, the coenzyme of lactic dehydrogenase, is reduced in ischemic heart muscle is consistent with this. If it is true that lactate is the preferential carbohydrate substrate for energy production in heart muscle, then a marked reduction in the content of coenzyme I as the result of anoxia might be significant in altering the function and even the viability of the ischemic tissue. If it is proved that the latter can be restored or improved by the administration of vitamins from which the necessary coenzymes are produced, an important observation will have been made. As yet, however, the observations of Govier have to be confirmed, their specificity in regard to cardiac function has to be demonstrated, and it remains to be shown whether the administration of nicotinamide, riboflavin, or succinate actually produces any beneficial effect on cardiac function.

COMMERCIAL PROCESSING AND THE BIOLOGIC VALUE OF FOOD PROTEINS

Interest has developed in the last few years in the question of how the nutritional value of proteins in foodstuffs is affected by processing and by storage. The most important factor causing change during processing is heat, and much information has been collected during the last twenty-five years upon the effects of heat on food proteins; but what its effect upon any given protein will be can be determined only experimentally, as there are no sufficiently comprehensive generalizations to permit us to make a prediction. Too great a heat will of course decrease the value of any protein, but a more moderate degree of heat may increase or decrease it, or have no effect at all. When the protein is improved, the effect may be due either to an increase in the digestibility of the protein, or to an increase in the biologic value, or to both.

Mitchell, Hamilton, and Beadles (*J. Nutrition* **29,** *13 (1945)*) have described measurements upon the proteins of soybean, coconut, and sunflower seed. It is well known that moderate heating increases the biologic value of soybean proteins, but these authors have made a quantitative comparison of the effect of different degrees of heat. In a first experiment they measured the effect of autoclaving soybeans of the Illini variety for one hour at 15 pounds steam pressure. This treatment increased the digestibility of the protein from 78 to 83 per cent, and the biologic value from 49 to 67 per cent, thus improving the food value of the beans considerably. The value of any food as a source of protein is perhaps best expressed as the "net protein value" defined by Mitchell and Carman (*J. Biol. Chem.* **60,** *613 (1924)*), calculated by multiplying the percentage of protein in the food, the digestibility of the protein, and its biologic value. (The last two items must be expressed as fractions of unity instead of percentages for this calculation.) The net protein value of the soybean was increased 45 per cent by the autoclaving in the experiment reported.

The authors also investigated the effect of the so-called gun-explosion process, as used for the preparation of some breakfast cereals, upon soybeans. Raw soybean flour was prepared by grinding the beans. "Exploded" flour was prepared by heating the beans in a closed chamber to about 550°F. for ninety seconds, then injecting steam into the chamber for one minute until the pressure reached 185 pounds per square inch, and finally releasing the pressure in the chamber instantaneously. A "partially exploded" flour was also prepared by similar means, using steam injection for forty-five seconds to a pressure of 165 pounds per square inch before release. For the raw, partly exploded, and fully exploded soybean flours, the digestibility figures were 85, 96, and 93 per cent respectively and the biologic values were 59, 75, and 71 respectively. Thus the partially exploded flour had a net protein value well above that of the raw flour, while the value of the fully exploded flour was intermediate. The more rigorous heat treatment of the fully exploded flour led to a product in which the protein had presumably been first rendered available and then damaged by the heat.

Mitchell, Hamilton, and Beadles also examined a coconut meal and a sunflower seed meal prepared by solvent extraction at low temperatures. In the commercial extraction of oil-bearing seeds attention is given chiefly to the yield of oil rather than to the quality of the residual meal, which is a valuable source of protein for stock feeding. Whether prepared by solvent extraction or by the expeller process, the meal is exposed to high temperatures which may reduce the value of the protein (except for soybean meal). For their studies the authors obtained specimens of the two meals which had been prepared by solvent extraction at temperatures never exceeding 75°C. The

sunflower seed meal protein had a digestibility and a biologic value of 94 and 64 per cent respectively; the coconut meal 86 and 71 per cent respectively, as compared with a biologic value of 58 per cent previously obtained for an ordinary commercial coconut meal. The proteins of these two meals compared in biologic value with the better cereals, and the digestibility of sunflower seed protein was higher than that of cereal proteins.

The authors emphasize the need to temper the heat processing of foods bearing valuable supplies of protein. For soybean protein they confirmed the beneficial effect of a heat treatment upon the biologic value, and showed that when the gun-explosion process was used less benefit was obtained at the higher of two temperatures tested. Stewart, Hensley, and Peters (*J. Nutrition* **26,** *519 (1943)*) had shown previously that the biologic value of oat protein is decreased by the gun-explosion process.

From their work on two types of oil seed meal, Mitchell, Hamilton, and Beadles conclude that if more care can be given to the preparation of such meals by mild, low temperature processing, they will deserve study to determine how far they can be introduced into human diets as sources of protein.

SPECIFIC EFFECTS OF DIFFERENT FATTY ACIDS IN CHOLINE DEFICIENCY

The production of fatty livers in the rat by feeding a diet low in choline and methionine is affected by a considerable number of the components of the diet. Previous articles in this journal (*Nutrition Reviews* **2,** *302 (1944)*; **3,** *182 (1945)*) dealt with a number of these, but did not consider the effects of the nature and amount of the fat in the diet. Channon, Hanson, and Loizides (*Biochem. J.* **36,** *214 (1942)*) showed that with a given type of diet the inclusion of saturated fatty acids led to the deposition of more fat in the liver than the inclusion of solid unsaturated acids. Also, in general, the more fat in the diet, the greater will be the deposition of fat, although under suitable conditions very fatty livers can be produced on diets containing no fat at all (Gavin and McHenry, *J. Biol. Chem.* **132,** *41 (1940)*).

Stetten and Salcedo (*J. Nutrition* **29,** *167 (1945)*) have studied the effect of the length of the carbon chain of the fatty acid in the diet on fatty liver formation when the acids are fed in the form of the ethyl esters at a level of 35 per cent in the diet. Each member of the homologous series of acids from butyric to stearic having an even number of carbon atoms in the molecule was tested for a two-week feeding period, and the results varied in a remarkable manner. There was a difference in toxicity of the acids: 2 rats receiving ethyl butyrate died, and 15 of 16 receiving ethyl laurate died, in the two-week period. One rat of 4 receiving ethyl stearate, and 4 of 9 receiving ethyl caprylate died; there were no deaths in any of the other groups.

There were wide differences in the amount of fatty acid found in the livers of rats which survived the experimental period. In the stearate group (3 rats) the mean liver fatty acid content was 3.2 per cent; in the palmitate group (4 rats) 9.4 per cent; in the myristate group (4 rats) 17.2 per cent; in the caprylate group (5 rats) 4.4 per cent; and in all other groups from 7.0 to 8.0 per cent. Thus it appears that myristic acid alone among the fatty acids tested leads to the formation of a definitely fatty liver when fed as the ethyl ester. In an accompanying paper by Kesten, Salcedo, and Stetten (*J. Nutrition* **29,** *171 (1945)*) the results obtained by feeding a lower level of ethyl laurate suggest that this ester too causes much fat deposition in the liver before it kills the rat. The data presented at once

raise a number of interesting new questions which will require new experiments for their solution. Do the fatty acids exert an equally great influence on fat deposition when fed as the ethyl ester on the one hand or as a triglyceride on the other? This question is posed particularly by the low liver fatty acid level produced by ethyl stearate. With a diet containing 15 per cent of casein and no choline, it might have been expected that the inclusion of any higher fatty acid triglyceride to the extent of 35 per cent would lead to a very fatty liver, yet in fact the mean figure observed when ethyl stearate was used was less than when all the fat of the diet was replaced by glucose.

This is a remarkable finding which calls for further inquiry. Some of the groups of rats were so small that doubt attaches to the results obtained with them, but the singularly powerful effect of myristic acid as compared with all the others, possibly excepting lauric acid, seems well established. As the molecular weight of the ester fed was decreased, from stearate to myristate, there was an apparent decrease in the mean equivalent weight of the liver fatty acids, but this result also seems to require more data in order to establish it soundly. However, the conclusion drawn by Stetten and Salcedo that "some of the discrepancies observed by several workers in the fatty liver problem are due to unrecognized variations in the composition of the dietary fat" is certainly now well established; it appears that some of the causative variations are still not fully defined.

Different immediate causes operated to produce death in the different groups. At autopsy of the rats which had received ethyl caprylate and died, it was found that the chief pathologic condition was renal necrosis and hemorrhage similar to that which has been described in choline deficiency by earlier workers. The 2 rats which were given ethyl butyrate both died within two days, their intestinal tracts full of blood arising from acute gastric ulceration and hemorrhage.

The rats which were given ethyl laurate died showing interesting heart lesions. Care was taken to exclude the possibility of any toxic contaminant of the lauric acid used for the synthesis of the ester, and the results described must be attributed to this compound itself. The cause of death was congestive heart failure, and the rats displayed no unusual symptoms before death, appearing to be normally active within two hours of death. Except for some deposition of fat in the livers, the other organs showed no histologic change except congestion. The heart lesion was an inflammatory myocarditis, which was shown by bacteriologic studies not to be due to invasion by microorganisms. The lesion was similar to the endocarditis of potassium deficiency, but an experiment showed that there was no less potassium in the heart or kidney than when sufficient choline was added to prevent the appearance of the myocarditis.

The addition of cystine, choline, betaine, or methionine to the diet in suitable amounts prevented death in rats receiving 35 per cent of ethyl laurate in the diet: also it was observed that 2 rats given a diet containing 25 per cent of ethyl laurate did not die within fourteen days, although autopsy at that time revealed a similar but much milder myocarditis.

A FIELD SURVEY OF NUTRITION

Johnson and co-workers of the Harvard Fatigue Laboratory (*War Medicine* **7**, *222, 227 (1945)*) present the results of a field study of nutrition and describe the ingenious field nutrition laboratory which they have devised. The laboratory weighs about

one ton and costs $3500, exclusive of labor. The following analyses can be made on urine: albumin, sugar, acetone bodies, thiamine, factor F_2, riboflavin, ascorbic acid, chloride, and nitrogen. On whole blood hemoglobin, hematocrit, dextrose, nonprotein nitrogen, carbon dioxide, carbon monoxide, oxygen, and dissolved nitrogen can be measured; on serum, total protein, chloride, ascorbic acid, oxygen, and carbon dioxide. Visual colorimeters and fluorometers are used in preference to photoelectric instruments, for practical reasons. A group of 4 trained men can complete a battery of observations including all the chemical analyses of blood and urine on 20 men in two days. One of these men is a medical observer trained in nutritional and biochemical work who obtains data on the medical history and performs physical examinations, as well as assisting in the chemical work; another is a technician trained in eliciting dietary histories; and the remaining 2 are technicians trained in all the specific methods outlined.

Johnson and co-workers now report the results of studies which were carried out in a temperate region (New England), in a desert during the summer (Mojave Desert), in a subarctic region in the winter (Saskatchewan), and in mountain regions in the summer (Colorado Rockies). They employed a system of diagnosis depending on consideration of (1) the detailed medical history; (2) a detailed dietary history; (3) a routine medical examination which stressed, in particular, inspection of the skin, eyes, nose, lips, gums, teeth, tongue, and nervous system and gave little attention to other parts of the body; (4) chemical examination of blood and urine obtained from the subjects before breakfast; (5) analysis of chemical changes resulting from the administration of a standard oral dose consisting of 500 mg. ascorbic acid, 5 mg. thiamine hydrochloride, 5 mg. riboflavin, and 50 mg. nicotinamide; and (6) performance of both short and prolonged tests of physical fitness for hard work. The urine was collected four hours following the oral dose of vitamins.

Certain physical signs were extremely common in the troops examined and were not necessarily related directly to the diet. The commonest included carious teeth, gingivitis, a coated tongue, and certain types of dermatitis as well as conjunctivitis, and alterations of tendon jerks and asymmetry of vibratory sense in the legs. Individual differences in absorption of vitamins and in renal threshold were wide. These investigators frequently found, in normal persons, high plasma levels for chloride or ascorbic acid with low urinary levels. They attached significance, as indicating unsaturation, only to a low plasma level with a low urinary level. Again, with respect to F_2 they often observed both low and high fasting levels with high excretion of the test doses, and also with low excretion. Therefore, they gave credence only to a low fasting level associated with a low excretion of the test dose.

A table is given for averages and ranges for substances estimated by the field methods, and the criteria used as indicating chemical inadequacy are outlined. These include, in respect to water inadequacy, a serum protein above 7.5 g. per 100 ml.; in regard to calories the presence of ketosis and sometimes hypoglycemia; with regard to salt they attached significance to a fasting serum chloride below 98 milliequivalents per liter, and fasting urine chloride less than 0.2 g. of sodium chloride per hour. Fasting serum ascorbic acid levels below 0.3 mg. per 100 ml. and excretion of less than 3 mg. in four hours after the test dose were interpreted as indicating inadequacy of ascorbic acid. With regard to thiamine they attached significance to a fasting urinary excretion of less than 0.6 microgram per hour and excretion after the test dose of less than 20 micrograms in four hours. As to riboflavin, fasting urinary excretion less than 20 micrograms

per hour and excretion after the test dose of less than 200 micrograms in four hours was considered significant. A fasting urinary excretion of factor F_2 less than 0.03 mg. per hour and excretion after a test dose of nicotinamide less than 0.5 mg. of factor F_2 in four hours indicated nicotinic acid inadequacy.

The approach of these investigators in general appears to be conservative. They stress that men in apparently good health can have low stores of vitamins and point out that supplementing normal diets with vitamins does not lead to significant increases in physical fitness. They have frequently seen severe loss of weight without undue caloric deficiency, desiccated skin without demonstrable dehydration, apparently identical neurologic changes in men with and without thiamine unsaturation, identical types of conjunctivitis and cheilosis with and without riboflavin unsaturation, similar reddening and atrophy of the tongue with low and with high urinary levels of factor F_2, and identical types of gingivitis with no ascorbic acid in the serum and with high levels of ascorbic acid in the serum. They have seen remarkably high physical fitness and morale in groups of men whose chemical stores were by orthodox interpretation low, and extremely poor physical fitness in groups of well saturated men. They have found adequate chemical stores in men subsisting on unbalanced diets, and low levels in those whose diets by analysis were high in water soluble vitamins. They indicate, therefore, that conservatism is desirable in making a diagnosis of nutritional deficiency.

In field studies certain time relationships must be considered. Johnson has reported (*Gastroenterology* **1**, *832 (1943)* that deprivation of water can kill a man in hot weather in a day or two, caloric deficiency can demoralize working men in two or three days, salt deficiency even in cold weather can lead to serious results in three or four days, and deficiency of the vitamin B-complex can result under some circumstances in chemical unsaturation in from one to two weeks with physical deterioration. In an individual given a previously normal diet, ascorbic acid deficiency can begin to cause trouble within three months. Diets can be low in protein, fat, and the fat soluble vitamins for several months however without serious effects.

These investigators have been impressed with the manifold and complex possible causes of physical deterioration which include emotional disturbances and uncomfortable or perilous surroundings, diseases that are not fully incapacitating, the rigors of work, environmental extremes, as well as combinations of many types of nutritional deficiency. Unless these complexities are recognized, serious errors of interpretation may arise in nutritional surveys.

THE FLUORINE PROBLEM IN LIVESTOCK FEEDING

Fluorine toxicosis in livestock has been a problem confronting feeders for a number of years. The problem developed largely as the result of the use of substitutes for bone meal as sources of phosphorus in mineral supplements to farm rations. Prominent among these substitutes are some of the phosphatic rocks which contain relatively large amounts of fluorine as compared with bone meal. Early investigations suggested the possible suitability of these phosphatic materials as sources of phosphorus but indicated, at the same time, the potential danger of their relatively high fluorine content. As a result, there was a limited use of these materials under conditions where it was felt that the fluorine hazard was not large.

A critical situation arose, however, with the advent of the war. Imports of bone

meal from South America were greatly reduced, while the demands for phosphorus supplements for feeding were markedly increased in proportion to the increased livestock production programs. The problem was resolved into one of satisfying the phosphorus requirements of the livestock population without undue risk of physiologic damage by fluorine.

In 1942, H. H. Mitchell prepared a report for the Committee on Animal Nutrition of the National Research Council (*National Research Council Reprint & Circular Series no.* **113** (*1942*)) in which the existing evidence was summarized with respect to the fluorine hazard in animal feeding. Subsequently a second report (*National Research Council Report no.* **10**, *Committee on Animal Nutrition* (*1943*)) was published in which the phosphorus requirements of livestock were critically appraised with the purpose of satisfying these demands and, at the same time, reducing fluorine hazards to a minimum.

The needs of farm animals for supplementary calcium and phosphorus are usually met under normal conditions by the use of a combination of limestone and bone meal, neither of which contains an appreciable amount of fluorine. Untreated phosphatic rock, on the other hand, usually contains from 3 to 4 per cent of this element. Treated rock phosphate, superphosphate manufactured from rock phosphate, and so-called defluorinated rock phosphate all contain less fluorine than the original raw rock, but in no instance has a fluorine free product been produced.

In farm animals suffering from chronic fluorosis, the appetite is reduced and the efficiency of food utilization lowered, resulting in impaired growth or loss of weight in mature animals. Milk production is lowered in dairy cattle. Unthriftiness, anorexia, and death follow the ingestion of relatively large amounts of fluorine. Most of the fluorine ingested by animals is deposited in the bones and teeth where striking changes take place. In the bones, isolated outgrowths of bony tissue often occur or there is a complete superficial covering of porous white bone of high fluorine content. The bones are, as a rule, much softer than normal but, owing to overgrowth, the breaking strength may be increased. The teeth are likewise affected, the first signs of incipient fluorosis being hypoplasia of the enamel during the formative period.

There may be a long period, of as much as a year in herbivora, during which the animal, while manifesting no outward symptoms, may be ingesting daily amounts of fluorine which will eventually prove toxic. During this time the skeleton is becoming gradually saturated until finally the absorbed fluorine can no longer be immobilized, and then exerts its general toxic effects. Accumulations of minute amounts of fluorine also occur in the soft tissues and may induce degenerative changes in the kidneys, liver, adrenal glands, heart, and central nervous system.

Mitchell states that the severity of tissue damage induced by fluorine depends upon the type of fluorine compound ingested, upon the dosage, the duration of exposure, and the calcium content of the ration. The question of the highest level of dietary fluorine that farm animals can safely ingest has not been answered satisfactorily. However, it appears that the lowest level of fluorine in the ration at which incipient symptoms of fluorosis may appear is somewhat less than 0.014 per cent for the pig, somewhat more than 0.011 per cent for sheep, somewhat less than 0.008 per cent for cattle, and between 0.035 and 0.070 per cent for fowls. Therefore the borderline between safe and unsafe amounts for these animals is about 0.01 per cent for all except the avian species, for which the amount is possibly of the order of 0.05 per cent. With the aim of providing more than borderline safety, and in recognition of a rather wide variability in the fluorine

content of minerals, it is proposed that permissible levels of fluorine be 0.003 per cent of the total dry ration for cattle, sheep, and swine, and 0.015 per cent for poultry.

In prewar years there was generally a liberal use of mineral supplements for livestock. In many instances this practice was justified but a critical appraisal of the facts leads to the conclusion that when protein and vitamin D are supplied in adequate amounts, the occasions when a phosphorus mineral is needed to supplement farm rations should be rather exceptional. This generalization does not apply to those geographic areas where the forage is characteristically low in phosphorus and where the feeding of steamed bone meal has proved to be necessary. Becker and co-workers at the Florida Agricultural Experiment Station (*Florida Agr. Exp. Sta. Bull.* **401** (*1944*)) have determined the conditions under which defluorinated superphosphate can be fed to beef and dairy cattle and swine and conclude that this material can be used satisfactorily when offered in appropriate form, i.e., when mixed with relatively higher proportions of common salt than are needed with bone meal.

Essentially, the process by which the fluorine content of natural phosphates may be reduced is one of heat treatment. Ellis and Cabell (*J. Animal Sci.* **3,** *446* (*1944*)) have investigated the biologic availability of some defluorinated natural phosphates with rats. They have concluded that none of the products they have studied is fully equal to bone meal as a source of phosphorus although some might be considered acceptable substitutes. Their tests suggest that the temperature of defluorination probably is the critical factor determining the availability of these phosphates to the animal. Tests on experimental batches of superphosphates defluorinated at temperatures of 600°, 760°, and 1010°C. showed a wide range of feeding value, the best products being produced at the higher temperatures. Natural phosphates containing considerable iron or aluminum were relatively unsatisfactory, presumably because the phosphorus was rendered unavailable by these elements.

Progress has thus been made in dealing with this problem, but the fluorine hazard has not been completely eliminated in the use of natural phosphatic rock products in animal feeding.

THE NICOTINIC ACID REQUIREMENT OF THE RABBIT

The rabbit has now been added to those species which must be furnished with dietary nicotinic acid, when it is fed upon simplified rations. Wooley and Sebrell (*J. Nutrition* **29,** *191* (*1945*)) have obtained nearly normal growth in rabbits maintained on their simplified diet for a limited period, and have demonstrated the onset of nutritional failure when nicotinic acid is omitted from the diet. The diet which they used contained casein, Wesson oil, sucrose, cellophane, and salt mixture, with the following supplements: carotene, vitamin D, alpha-tocopherol, choline, nicotinic acid, inositol, vitamin K, pyridoxine, thiamine, riboflavin, and pantothenic acid. It was found necessary to train rabbits to eat such a diet.

In an initial experiment it was shown that 10 week old rabbits placed on this diet gained in sixteen weeks almost as much weight as others of the same strain fed a stock ration. Pairs of litter mates were then used to determine the effect of omitting nicotinic acid from the ration. The rabbits receiving no nicotinic acid lost weight, on the average, over a period of nineteen weeks, while their controls receiving nicotinic acid grew normally. During the experimental period 7 of the 11 rabbits fed the deficient diet died, showing emaciation

and terminal diarrhea. No significant changes in the buccal mucosa were seen, and the only consistent findings at autopsy were liquefaction of the fecal matter and gaseous distention of the intestines.

In order to establish whether these signs were due directly to nicotinic acid deficiency, a further experiment was performed in which the control rabbits receiving nicotinic acid were pair-fed with the experimental rabbits. Each pair was observed until one rabbit died, the other was then killed for autopsy; out of 6 pairs, 3 rabbits on the deficient diet and 3 on the complete diet died before their mates. All the rabbits which died showed the symptoms described above, whatever their diet had been, suggesting possibly that these symptoms and signs were due only indirectly to nicotinic acid deficiency, being in fact directly produced by slow starvation. Extensive histologic examination of the tissues disclosed no consistent lesions attributable to nicotinic acid deficiency. The nicotinic acid content of liver, skeletal muscle, and kidney was determined microbiologically, and in skeletal muscle was found to be significantly lower in the deficient rabbits, when the diets had been fed for fifteen weeks or longer.

Data were obtained for the requirement of the rabbit for this vitamin by feeding the deficient diet and dosing the rabbits with nicotinic acid separately. When 0.2 mg. or less nicotinic acid per kilogram was given, the rabbits showed a steady but slight loss of appetite, and only if they received as much as 0.2 mg. were they able to increase their weight very slightly. With 0.5 or 1.0 mg. per kilogram, the food consumption remained stable, and steady but submaximal growth occurred. With 5.0 or 10.0 mg. per kilogram, food consumption definitely increased and growth was apparently approaching the maximum rate.

This study adds much to our knowledge of the comparative biochemistry of nicotinic acid. It poses the interesting question of why fatal nicotinic acid deficiency in the rabbit is accompanied by no symptom or sign more specific than anorexia. It is possible that for the development of any changes in the rabbit comparable to those seen in a man with pellagra or in a dog with blacktongue, the diet must not only lack nicotinic acid but possibly also furnish corn products, and it is to be hoped that new experiments will soon decide this point.

THE UTILIZATION OF SUCROSE

It seems logical to suppose that glucose administered to man would be a better source of energy for immediate muscular work than sucrose. Glucose is the "physiologic" sugar since this is the form which occurs in the blood stream, while sucrose in the blood stream would be completely excreted. One might expect that the hydrolysis of sucrose required in the intestine before absorption would delay its utilization in the body. This view has persisted in spite of Higgins' (*Am. J. Physiol.* **41,** *258 (1916)*) observation that when the sugars were given orally, sucrose caused a marked rise in the respiratory quotient within four minutes, while with glucose the rise was observed only after twenty minutes. A similar result has been noted by a number of subsequent investigators who were interested in the means by which the respiratory quotient is raised. In experiments of a longer term nature, Deuel, Gulick, and Butts (*J. Biol. Chem.* **98,** *333 (1932)*) demonstrated that sucrose is a more effective antiketolytic agent than glucose against the ketosis of fasting.

Rabinowitch (*J. Nutrition* **29,** *99 (1945)*) has reinvestigated this question with a dif-

ferent technic. His experimental criteria consisted in the subjective response and the rise in blood sugar of diabetic patients suffering mild hypoglycemia induced by insulin overdosage, after they were given sucrose. Clinical experience has led him to advise diabetic patients to carry cubes of sucrose and to eat these to combat mild insulin reactions. This treatment was found to be satisfactory; only after very severe reactions was it necessary to administer glucose but this was by intravenous means.

For his observations, Rabinowitch chose a number of patients who were being treated with protamine zinc insulin and who suffered hypoglycemia in the morning before breakfast. A blood sample was taken and the subject given 10 g. of sucrose dissolved in 200 ml. of water. Further blood samples were drawn for sugar analysis at one minute intervals until the patient stated that he felt better. Only those subjects were reported in whom a response was obtained in a few minutes, since failure to respond rapidly permits no possible deduction about the rate of hydrolysis and absorption of the sucrose, as it is well established that severe insulin hypoglycemia may require treatment with hundreds of grams of sugar before the blood sugar will rise.

In the fasting state, the average blood sugar level in 10 subjects was 56 mg. per cent; in only 3 subjects was it above 60 mg. per cent. Following the drinking of the sucrose solution, a marked rise in the blood sugar was noted in all subjects within five minutes; it appeared within one minute in 2 subjects. Care was taken to prevent "emotional" increase in the blood sugar level. It is clear that the hydrolysis of sucrose must be rapid, so that it does not delay the availability of the sugar. The idea that the "physiologic sugar" glucose is superior to sucrose as a source of immediate energy finds little confirmation in the experiments described. Perhaps as significant as the practical import of this work is the demonstration that an apparently logical extension of known facts is not always a safe procedure.

FACTORS AFFECTING THE VITAMIN CONTENTS OF PLANT PARTS

The increasing interest in the vitamin content of foods has encouraged the investigation of possible effects of various environmental and hereditary factors upon the amount of vitamins produced in plants ordinarily used as human food. It has also prompted numerous surveys of hitherto neglected parts of ordinary food plants and of parts or organs not now in common usage as human food.

A survey of several garden vegetables has been made by Pepkowitz, Larson, Gardner, and Owens (*Plant Physiol.* **19,** *615 (1944)*), especially with respect to variety and stage of maturation. The ascorbic acid concentration among individual plants of a given variety varied considerably in contrast to carotene values, which were more constant within each variety. In green peppers no significant variation in carotene content was found among ten varieties, but consistent differences in ascorbic acid content have been demonstrated during several seasons. As fruit size increases with growth, carotene decreases and ascorbic acid increases. Ascorbic acid was found more abundant in the external portions of the fruit, in agreement with much work on other fruits. During ripening to the red stage, the carotene concentration increased thirty-two fold, attaining values as high as 200 micrograms per gram. Such high values might make red peppers valuable food supplements if a high carotene content could be made consistent and retained during processing.

The average corresponding ascorbic acid increase was 50 per cent.

In the case of garden peas, six varieties showed no significant differences. Overmature peas retained their carotene but lost considerable ascorbic acid. Wider spacing of plants in the row led to a 16 per cent increase in ascorbic acid content but decreased the yield so much that it would not be economically important.

Beet tops contain two and a half times as much ascorbic acid as the roots, with significant differences between varieties (tops). Carotene contents were uniform. No uniform change with maturation was found. Only one-twelfth as high a concentration of ascorbic acid occurs in the petiole as in the leaf blade, so that the petiole may be discarded with little loss.

Ten varieties of carrots showed significant varietal differences and all increased in carotene content with maturation. At the best marketable stage, an average for all varieties at ninety days from planting, the carotene content was at a maximum. A week later the content had appreciably decreased. A significant inverse relationship was found between average size of the roots and carotene content. No association was apparent between the ratio of diameter to length and the carotene content.

Platenius (*Plant Physiol.* **20,** *98* (*1945*)) has investigated diurnal and seasonal changes in the ascorbic acid content of snap beans, broccoli, kale, spinach, and Swiss chard. Samples were picked in early morning and evening. When expressed on a fresh weight basis, results indicate a slightly higher content of ascorbic acid in the late afternoon than in the early morning, but this difference was caused by diurnal fluctuations in the water content of the plants. On the dry weight basis, no consistent differences were found. A constant value was found over a five day period for kale and spinach. A single day of rainy weather has no effect on the ascorbic acid content. In kale, the content declined only about 20 per cent from July 29 to October 26, even though weekly averages of daily solar radiation decreased 76 per cent. The corresponding average temperature drop probably counteracted in part the effect of lowered light intensity. Under field conditions during summer months, periods of low light intensity usually coincide with periods of relatively low temperatures. Since these two factors have opposite effects on ascorbic acid content of plants, the time of picking vegetables during the day is probably unimportant in field practice, so far as ascorbic acid is concerned.

Sprouted legume seeds contain protein of high biologic value and are in many cases fairly palatable. Since they could be made available in large quantities, it is important to know the changes in vitamin contents during germination. Burkholder and McVeigh (*Plant Physiol.* **20,** *301* (*1945*)) studied this problem in Canner King peas, the Mung bean commonly used in chop suey, and 7 varieties of field type soybeans. On a dry weight basis, niacin, pantothenic acid, inositol, biotin, riboflavin, and ascorbic acid increase greatly during germination. Thiamine and pyridoxine contents remain unchanged, and vitamin Bc content decreases. A few varietal differences are apparent among the soybeans studied. Mung beans are inferior to soybeans in thiamine and biotin, but far superior in riboflavin, niacin, and vitamin Bc contents. The eightfold increase in ascorbic acid content during germination made the Mung bean outstanding, as was the case also for riboflavin. Peas showed the greatest increases in pantothenic acid and niacin. Field varieties of sprouted soybeans seem richer in vitamins than do the garden varieties. The use of sprouted seeds in canning and dehydration would permit operation on a twelve month basis. Judging by the content of these vitamins and available amino acids, it appears that the use of sprouts in the diets of Oriental peoples

rests on a sound nutritional basis and might be applicable in other parts of the world.

Burkholder and McVeigh (*Plant Physiol.* **20,** *276 (1945)*) also studied the B-vitamin contents of buds and shoots of 18 common tree and woody plants. When winter buds begin to expand and grow, the activity is similar to that in germinating seeds from the energistic point of view, and similar vitamin changes might be expected. The rest of the plant may aid in supplying vitamins to the growing points. In most cases the vitamin contents (expressed on a dry weight basis) increased during the period of bud expansion and shoot development. Browsing animals and birds which may feed on buds and shoots can obtain a considerable quantity of vitamins from this source, a fact which may be important in the conservation of wild life.

McVeigh (*Bull. Torrey Botan. Club* **71,** *438 (1944)*) made similar studies on various parts of small oat seedlings. The entire seedlings, grown in the dark for five days, increase greatly in niacin and riboflavin contents but remain constant in thiamine content per seedling. Thiamine and riboflavin are concentrated in the embryo, which constitutes one fifteenth of the dry weight of the endosperm. The leaf shows absolute increases in all three vitamins, and may be the center of vitamin synthesis.

THIAMINE STATUS DURING PREGNANCY

Many of the procedures for assaying nutritional status are of much greater value in determining probable normality than in demonstrating deficiency. From this viewpoint the study by Siddall and Mull (*Am. J. Obst. Gynec.* **49,** *672 (1945)*) is significant. These workers measured thiamine excretion in the urine of 42 pregnant women during various periods of pregnancy. Measurements were made by the thiochrome procedure, using the technic described by Wang and Harris (*Biochem. J.* **33,** *1356 (1939)*). There were two groups of patients; the first consumed a well balanced diet which included milk, cheese, eggs, meat, two leafy vegetables daily, fruit, and cereals; the second group consumed a similar diet together with a specified amount of thiamine daily, 0.75 mg. in some instances and 1.50 mg. in others. The average twenty-four hour thiamine excretion in the women consuming the normal diet without thiamine supplementation was 286 micrograms during the first trimester, 263 during the second, and 249 during the third. Those receiving supplements of thiamine excreted, as might be expected, larger amounts; namely: 478, 620, and 483 micrograms in each of the three trimesters, respectively, in the case of those consuming 0.75 mg. thiamine daily, and 932 and 1131 micrograms in the second and third trimesters, respectively, in those taking 1.50 mg. thiamine daily.

According to Melnick (*J. Nutrition* **24,** *139 (1942)*) a normal adult consuming a well balanced diet furnishing 0.86 mg. thiamine daily excretes more than 200 micrograms of thiamine in twenty-four hours. In comparison, the findings in the pregnant women even in the last trimester were satisfactory even when no thiamine supplement was used. The persons observed were all well and gave birth to normal, well developed, and well nourished infants. The blood pressure reading and the routine urine examination showed no abnormal findings. These observations are reassuring since much has been written concerning the greater requirement for vitamins during pregnancy and such increased requirements have been used as an argument in support of the thesis that vitamin supplementation is necessary. It would appear from this study that the taking of a well balanced diet serves nutritional purposes well.

THE WARTIME FOOD POLICY OF BRITAIN AND THE NATIONAL HEALTH OF SCOTLAND

L. S. P. Davidson, member of the Food Rationing Advisory Committee and Medical Referee for priority rations for Scotland, has presented an account of the food policy in Great Britain during five years of war and the effect of that policy on the nation's health (*Edinburgh Med. J.* **51,** *430 (1944)*). According to this writer two thirds of Britain's prewar food supply was imported and hence drastic measures were required to circumvent the gross deficit of meats, fats, cereals, dairy products, fruits, and vegetables. These measures were planned on a scientific basis giving due consideration to the experiences of World War I. The government's food policy centered about three objectives: (1) maintenance of the caloric value of the nation's diet; (2) maintenance of milk production; (3) increased home production of green and yellow vegetables.

The governmental actions designed to attain these objectives were: (1) The use of land for the production of food crops which were to be used directly for human consumption was increased with concentration on the production of cereals and potatoes. (2) Control of the ploughing-up policy on dairy farms was instituted and highest priority was provided in the issue of feeding stuffs to dairy farms. Rations for beef cattle, pigs, and poultry were markedly restricted. Further, the diversion of liquid milk to manufacturing purposes was prohibited. (3) Subsidies were provided, prices were stabilized, and home gardens were encouraged in order to increase the production of vegetables.

The necessary food imports, curtailed by the shortage of shipping space, were governed not only by a consideration of the nutritional values of the food but also from the point of view of storage, transportability, and geographic origin. First priority was reserved for wheat, second priority for fats, and third for cheese. Importation of meat and fruit was curtailed. The bulk of the foodstuffs was reduced where possible by compression and dehydration (e. g. milk, fruit juices, eggs, meat) and by deboning of meats. The extraction rate of wheat was increased from 70 per cent to 85 per cent (National wheat meal), thereby obtaining a greater yield of flour which was also of greater nutritional value.

The effects of this policy on the dietary are presented in a table showing the estimated supplies of nutrients available for civilian consumption per capita. The percentage change in 1943 as compared with prewar supplies showed minor decreases in calories (−5 per cent), animal protein (−7 per cent), fat (−13 per cent), and carbohydrate (−2 per cent). Increases occurred in vegetable protein (+23 per cent), total protein (+7 per cent), calcium (+52 per cent), iron (+27 per cent), ascorbic acid, thiamine, riboflavin, and niacin (gains of 13, 60, 30, and 3 per cent respectively). Davidson comments that "although the war-time diet is monotonous, it is adequate in so far as calories and protein are concerned and is superior to the pre-war diets in respect of the minerals, calcium and iron, and the vitamins of the B-complex. Only in respect of vitamins A and C is there any reason to suspect its adequacy."

Special measures were introduced to give priority supply of food to those persons whose demands were greatest because of growth, pregnancy, or illness. These included: (a) distribution of vitamins A, C, and milk to pregnant and lactating women and to children under 5 years of age; (b) the allowance of more meat for expectant and nursing mothers; (c) the institution of feeding programs through schools, industrial canteens, and the British restaurants; (d) the allowance of extra ration points and special priorities to the ill; (e) compulsory addition of vitamins A

and D to margarine, and of calcium to national flour.

The effects of the five years of altered dietary habits on the national health of Scotland is considered by Davidson under several headings. He first notes that despite the many difficulties of wartime "the productivity per head of population in Great Britain is stated to be the highest in the world." A review of the available data on the height, weight, and growth of children is stated to reveal a "highly satisfactory state of affairs." Except for tuberculosis and venereal diseases the incidence of the majority of the common infectious diseases was less in 1944 than before the war. It is suggested that the increase in tuberculosis was at least as much due to the unhygienic conditions of overcrowding as to any dietary influence. During the war period there has occurred, in Scotland, a reduction in infant mortality, in stillbirths, in the neonatal death rate, and in the maternal death rate. One may conclude, therefore, that vital statistics in Scotland show that the imposed dietary restrictions have exerted no adverse influence on the health of the population. Furthermore, frank deficiency disease is as rare now as in the prewar era. Davidson feels that mild anemia is still common in infants and women but that "its degree and frequency are certainly no greater (and possibly less so) than before the war."

The effect of wartime changes on the diet of different sections of the population is set forth as follows: "(1) The more fortunate members of society whose diet was formerly unrestricted by economic circumstances have had their intake of many of the essential nutrients reduced as a result of war, but the evidence adduced regarding national health shows that these reductions have done no material harm. In the small proportion of people who consistently ate and drank too much, there has probably been an actual improvement in health; (2) improved economic circumstances, the more even distribution of essential food-stuffs brought about by rationing, the introduction of national flour, and the fortification of certain foodstuffs have certainly prevented any further deterioration in the diet of the less fortunate section of the population who, before the war, could not buy an adequate diet, and in certain categories at least (*viz.* pregnant women, infants, and school children) have led to an undoubted improvement." (*See Nutrition Reviews* **1**, *112*, *173* (*1943*).)

Finally, Davidson concludes that "the success of the Government's wartime food policy can be attributed largely to the sound scientific basis on which it was founded. It is to be sincerely hoped that those wartime measures which have been shown to be of such value to the people's health, *i.e.* priority rations of milk for infants, school children and pregnant women, school meals and work canteens, National wheat meal bread, etc., will be continued as part of the permanent peacetime food policy."

This example of governmental planning from England may well serve as a pattern for international planning for the application of the science of nutrition to the difficult feeding problems to be met in the whole of Europe and in the Far East in the days to come. For, as Marrack has warned ("Food and Planning," *p. 265*, *Victor Gollancz, Ltd., London* (*1943*)), "if we do not plan for peace with a fairer distribution of the resources of the world, we must plan for war. But plan we must."

NUTRITION IN NEWFOUNDLAND

The report of a medical survey of nutrition in Newfoundland conducted in August, 1944, by nutritionists from Canada, the United States, and England has just been published (Adamson *et al.*, *Canad. Med. Assn. J.* **52,** *227 (1945)*). A unique feature of this study was the participation and accumulated opinion of workers from nine different governmental agencies or institutions from three countries. Thus the report has definite value in pointing out rather sharply the varying interpretations that have arisen from clinical studies by different authors. Such a collaborative effort emphasizes the widespread interest in nutritional problems and should point the way toward a better understanding between workers in this difficult field.

Newfoundland is an island in the Gulf of St. Lawrence, with an estimated population of 320,000. A large proportion of the population is distributed in some 1500 tiny settlements along the 6000 miles of coast. Many of these settlements are isolated in winter and, at best, means of communication are restricted. The island is to a large extent a "one-crop area with all the regrettable consequences." This "one-crop" is fish. However, farming, timbering, mining, and local manufacturing do contribute to the livelihood of a sizable number of the inhabitants. The war has not been without impact on the economic condition of the country. For example, the number of persons on relief has declined from 60,914 in 1940 to 7911 in 1943.

The general health of the population "is far from satisfactory" as indicated by a crude mortality rate per 1000 population of from 11.7 to 12.5 for 1939 to 1943. Comparable rates in Ontario were 10.0 to 10.4. The infant mortality rate is given as some two to three times that encountered in the United States or in Canada. The incidence of active pulmonary tuberculosis is estimated at the high level of 7 per cent. No statement is made in this report as to the availability of medical and dental services on the island or the possible role of these factors in bringing about this unpleasant picture.

The population sample which was examined consisted of "868 unselected people in St. John's and several outports who voluntarily submitted to examination after word of mouth publicity had been given as to the time, place, and purpose of the examination." The manner described for obtaining the individuals to be examined may not have led to a random sample and perhaps resulted in one loaded with persons who felt the need of medical attention and so were less unwilling to submit to such an examination.

General clinical impressions were that the average person observed was slow in mental reactions, lacking in initiative, seemed older than his age, and possessed an inelastic, frequently atrophied and wrinkled skin. Poor muscular development was often encountered and "minor stomach ailments and severe constipation were very common." The results of the detailed account of various physical defects noted, the laboratory findings, and the data on nutrients available for civilian consumption per day in 1943 may be summarized under the respective headings of specific nutrients below:

Calories: Although 2997 calories were reported as available per day per capita, the population could be described as a "lean one" in that 30 to 43 per cent of the subjects were more than 10 per cent underweight. How much of this could be attributed to diseases other than those of nutritional origin is not stated. Seven to 9 per cent of the examinees were 10 per cent or more overweight. The children were not short of stature as compared with widely used standards. The food available seemed to be adequate in calories but from the weight data it appeared that the distribution of these calories among the population could be improved.

Fat: Eighty g. of fat per capita per day were available. This constituted approximately 23 to 24 per cent of the total calories, a figure sufficient for health but less than that consumed by people in the United States and Canada.

Protein: The estimated available protein (88.4 g.) was greater than the Recommended Allowances of the National Research Council. No clinical evidence of protein deficiency was found, but laboratory data indicated a satisfactory range of serum protein values.

Thiamine: Florid beriberi, once prevalent in Newfoundland (Little, *J. Am. Med. Assn.* **58,** *2029 (1912);* **63,** *1287 (1914)*), was not encountered in this survey. Neurologic changes were observed in 6.8 per cent of the examinees. However, the nonspecificity of these signs, especially among older persons, must be recognized. The urinary thiamine excretions indicated a relatively low intake of this essential. The dietary thiamine (0.9 mg. per day) is above the level which might be expected to produce symptoms in a diet containing more than 20 per cent fat and would be considered by some as an adequate intake (McHenry, *Canad. Med. Assn. J.* **52,** *147 (1945)*).

Riboflavin: Dietary riboflavin was estimated at 1.03 mg. per day and the studies of the excretion of riboflavin in the urine would confirm this level of intake. Signs resembling ariboflavinosis occurred in from 6.2 to 68.7 per cent of the subjects. Since no correlation was found between these observed clinical signs and the riboflavin excretion in the urine, it is impossible to arrive at an accurate estimate of the incidence of riboflavin deficiency.

Niacin: A high dietary intake of niacin (15 mg. per day) was reported and pellagra was not encountered. Despite this, the tongue changes seen were interpreted to indicate that "mild acute and mild chronic niacin deficiency is a frequent occurrence in the population examined."

Ascorbic Acid: The ascorbic acid content of the diet was estimated at between 20 and 48 mg. per day. The serum ascorbic acid levels of 28 per cent of the subjects were less than 0.2 mg. per 100 ml. No scurvy was observed. Gum involvement, held by some (Kruse, *Milbank Memorial Fund Quart.* **20,** *290 (1942); Nutrition Reviews* **1,** *118 (1943);* **3,** *44 (1945)*) to be specific for ascorbic acid deficiency, was encountered in 69 per cent of the population examined. This may be compared with a similar figure of 51 per cent for a North Carolina population with a mean vitamin C intake approaching that of the recommended dietary allowance (Milam and Darby, *South. Med. J.* **38,** *117 (1945)*). The authors concluded: "The clinical evidence indicates a high prevalence of deficiency of ascorbic acid."

Vitamin A: An estimated intake of 1443 I.U. of vitamin A was consistent with the serum measurements of this factor. The mean serum vitamin A levels were lower than those found in a group of children from a New York school. Skin changes resembling avitaminosis A were frequent as were conjunctival thickenings. The interpretation of these data would be facilitated by comparison of the values with those reported by Hsu (*Chinese Med. J.* **61,** *238 (1943); Nutrition Reviews* **3,** *38 (1945)*) for individuals with phrynoderma or xerophthalmia as clinical evidence of vitamin A deficiency. The evidence led the authors to conclude: "These data indicate a high prevalence of avitaminosis A."

Vitamin D: The absence of vitamin D deficiency was supported by both the infrequent finding of clinically detectable rachitic changes and the low phosphatase values. This satisfactory state was attributed to the wide use of irradiated evaporated milk and the feeding of cod liver oil to children.

Iron: The iron intake of 9.5 mg. would not

lead one to expect a high incidence of iron deficiency anemia. Without an age and sex division of the hemoglobin levels it is difficult to evaluate their significance from a nutritional standpoint, but it does not appear that iron deficiency is a major nutritional problem here.

This paper is accompanied by twenty-four excellent colored illustrations, which constitute an important contribution of the report. These depict the changes in the skin, eye, lip, tongue, and gums upon which the various diagnoses were based, and aid considerably in permitting experienced observers to evaluate the lesions discussed. The lesions depicted are not considered by all investigators as prima-facie evidence of specific deficiencies. This is illustrated by the following statement which appears in the paper: "While it is generally recognized that nutritional inadequacies will produce most of them (the lesions), some observers believe that some of them may also be produced by other means. Furthermore, some of the authors consider that even when the signs and symptoms are proved signs of nutritional ill health, they may not be so specific in their etiological relationship as is implied in the . . . presentation. Platt (one of the authors—Ed.) considers that the above comment is referable particularly to the conjunctival changes discussed under vitamin A and the tongue changes under niacin." Further, the critical reader will note that many clinical conditions are listed, the possible relationship of which to malnutrition has not been established, such as crackled skin, telangiectasis, suborbital pigmentation, blepharitis, and "staring" hair.

The unsatisfactory general health of this population cannot be attributed entirely to dietary habits on the basis of evidence presented here. The availability of medical and dental services must surely be a factor in the high death rate from tuberculosis, high infant mortality rate, and the striking state of dental health. However, the authors were in agreement that "the poor nutritional status of the people of Newfoundland may well be in large part responsible for their impaired health and deficiency."

The dietary data and the laboratory findings establish that the population of Newfoundland subsists at a definitely lower intake level than the population of Canada and the United States. There is a high incidence of minor physical changes which have been suggested to be related to the nutritional state of the individual. The significance of these changes cannot be evaluated at present. Our understanding of the significance to health of such signs would be greatly improved if it were possible to follow objectively the results of induced dietary changes among the population of relatively isolated regions such as are described in this report.

PROTEIN METABOLISM DURING CONVALESCENCE AFTER TRAUMA

In a previous review (*Nutrition Reviews* **3,** *86 (1945)*) recent observations on nitrogen loss following trauma were discussed. Studies were described which showed that in healthy patients with fractures a reaction is set up, in response to the trauma, which results in vigorous protein catabolism with losses to the organism of the nitrogenous portion of large amounts of body protein. Howard (*Arch. Surgery* **50,** *166 (1945)*) discusses these observations further and describes additional characteristics of "the protein catabolic process."

Study has indicated that the nitrogen deficit is brought about by increased excretion of nitrogen in the urine. Unless complicating gastrointestinal lesions occur there is no more than a normal amount of nitrogen

in the stools, thus the reaction does not involve an abnormality in the intestinal absorptive mechanism. It appears further that distribution of the nitrogenous portion of the catabolized protein after trauma follows the same pattern as in health, since urea and ammonia accounted for 85 per cent or more of the urinary nitrogen. Excretion of creatinine was unchanged.

This negative nitrogen balance has been observed not only following fractures and osteotomy but also in patients with burns or various types of infection, including meningitis and virus pneumonia (Peters, *Federation Proceedings* **3,** *197 (1944)*), empyema and wounds of the chest, and even in patients suffering from induced malaria. Fever *per se* does not appear to account for the reaction. Many patients with fractures showing this metabolic abnormality were free of fever, and the patients with malaria excreted far more nitrogen than could be accounted for by a 7 per cent increase in total metabolism for each degree of elevation of temperature.

The distinction between the protein loss following trauma and that following simple starvation is stressed. The latter type of loss of nitrogen can be appreciably reduced by feeding carbohydrate and is quickly stopped by giving a diet which provides adequate calories and protein. In healthy persons after trauma, on the other hand, high caloric diets with large quantities of protein often do not appreciably spare the body protein at the height of a vigorous protein catabolism reaction whether the protein is administered orally, or intravenously as amino acids. It has been noted, however, that plasma protein seemed to act as an efficient nitrogen sparing agent, even when vigorous protein catabolism was taking place.

Another difference is found in relation to potassium metabolism. In starvation, after the initial large output of potassium that presumably accompanies utilization of glycogen, the losses of nitrogen and potassium remain constant at a ratio of approximately 10 to 1 which is the proportion in which these substances occur in muscle protoplasm. However, during vigorous protein catabolism after fracture, when the patients were adequately fed, no coincident loss of potassium was observed but a positive potassium balance often occurred even during the period of greatest loss of nitrogen (Howard, *Tr. Assn. Am. Physicians* **58,** *162 (1944)*).

It seems reasonable to assume that the main source of the lost nitrogen must be the body tissue, the protein of the cells. Howard suggests that the same "available" nitrogen stores are called upon and sacrificed in this reaction as are used to replenish plasma protein when this element is constantly removed from dogs, as in the experiments of Whipple and Madden (*Medicine* **23,** *215 (1944)*).

Why these metabolic changes should occur and what purpose they accomplish is a complete mystery. It is reasonable to assume that the catabolic reaction has some valuable functional effect. It is no doubt significant that a similar catabolic process has not been observed, at least in the same degree, in persons who are poorly nourished. The vigor of the protein catabolism appears to depend on two factors, namely, (1) the intensity of the stimulus and (2) the capacity of the organism to respond to the stimulus. Possibly other factors also are concerned, such as a principle of the adrenal or the pituitary gland as suggested by Albright and Browne (*Minutes Fourth Conference on Metabolic Aspects of Convalescence, Josiah Macy Jr. Foundation, p. 22 (1943)*).

NOTES

Letter To The Editor

Dear Sir:

I wish to make a minor correction in the statement about some of our work, which appeared in the May NUTRITION REVIEWS, page 132, second column:. . .Daft, Robscheit-Robbins, and Whipple. . ."later demonstrated that when larger amounts were injected, a large loss of nitrogen occurred in the urine with resultant negative nitrogen balance."

This statement is somewhat misleading because in practically all the tables of that paper, positive nitrogen balance was shown and it was explained that the negative balance was due to lack of carbohydrates and fat. In a recent publication, Miller, Robscheit-Robbins, and Whipple, *Journal of Experimental Medicine*, February 1945, Table 1, a very complete experiment was reported showing a strong positive nitrogen balance, weight balance, and perfect clinical condition, when large amounts of plasma protein were given parenterally. We have dozens of these experiments now of that nature.

Occasionally others have reported negative nitrogen balance, but Elman's experiments are to be explained by the presence of citrate which is toxic. All our experiments were done with heparin as an anti-coagulant. I think there is no question but what plasma protein as plasma is the most effective way to bring about parenteral nutritional balance.

Very truly yours,
G. H. Whipple, M.D.,
Professor of Pathology,
University of Rochester School of Medicine and Dentistry,
Rochester, New York.

Carotenoids and Vitamin A in Milk Fat Globules

Henry, Kon, Gillam, and White (*J. Dairy Research* **10**, *114* (*1939*)) observed some years ago that the concentration of carotenoids was smaller in fat from churned milk than in the fat from the original milk. The vitamin A content was the same.

Kon, Mawson, and Thompson (*Nature* **154**, *82* (*1944*)) have shown that the explanation for this difference is not due to a destruction of carotenoids by the churning of the milk, but must rather be attributed to the relatively high concentration of carotenoids in the fat of the separated milk or in the whey. Determinations of carotenoids and vitamin A were made at different stages of butter making or preparation of cheese. Samples obtained during the separation by gravity of cream from milk were also examined. The investigators found that although the vitamin A concentration was the same in all the fractions, the fat of separated milk contained seven times, and the fat of separated whey, eleven times as much carotenoids as the fat of the original milk.

The investigators then measured the size of fat globules in the different fractions. The measurements showed that the size of the fat globules in those fractions which contained the highest carotenoid concentrations had the smallest diameter, whereas those of the carotenoid poor fraction had the largest diameter. Thus, the fat globules in the separated milk had a radius of 0.51 micron and contained 65.4 micrograms of carotenoids and 36 micrograms of cholesterol per gram of fat, whereas the fat globules of the cream had a radius of 1.68 microns and contained only 9.5 micrograms of carotenoids and 2.8 micrograms of cholesterol per gram of fat. Since carotenoids and cholesterol occur in large concentration in the small fat globules having a relatively larger surface, the authors suggest that those two compounds are mainly confined to the fat globule membrane, whereas vitamin A is in true solution in the fat. This may not be the whole explanation, however, since the

smaller sized particles contained, relative to their surface area, more cholesterol and carotenoids than did the larger particles.

Vitamin C in Wild Growing Plants

The search for wild growing plants rich in vitamin C is an old one, but one which receives great impetus with the blockade methods of modern warfare. Fortunately the present analytical methods for the vitamin make such a search both simple and practical.

The phenomenal amounts of vitamin C in rose hips, in the leaves of common evergreens, and in green walnuts have been previously reported (*Nutrition Reviews* **1,** *53, 246, 319 (1942–43);* **2,** *287 (1944)*).

Nyrop (*Ugesk. f. laeger* **100,** *644 (1938)*) has reported that berries of the barberry plant (Berberis polyantha) contain almost 50 per cent more ascorbic acid than an equal weight of lemon juice. The Indian gooseberry was found to contain 500 mg. or more of ascorbic acid per 100 g. of fruit, and the vitamin seems to be well preserved in the desiccated fruit (Srinivasan, *Nature* **153,** *684 (1944)*). Gooseberries are already being used as a vitamin C source for the Indian fighting forces.

The Eskimos, particularly in East Greenland, are exposed to a climate which certainly does not permit the growth of much vegetation, not to speak of the length of the winters. Many have wondered how these people obtained sufficient ascorbic acid to protect them against scurvy. Dr. A. Hygaard, who spent one winter in Angmassalik (cf. Christiansen, *Ugesk. f. laeger* **100,** *205 (1938)*) reported that the marine algae represent the most important source of ascorbic acid for the Eskimos during the winter, and apparently afford protection against scurvy since this deficiency was rarely observed. The algae contain between 20 and 30 mg. of ascorbic acid per 100 g.

It is apparent that extensive use is being made of the leaves and the fruits of wild growing plants as a source of ascorbic acid in a number of countries which do not have access to lemons or oranges. In fact, this vitamin is so generally present in wild growing plants that it seems likely that a supply at least sufficient to meet emergencies might be found in almost any section of the world.

Recent Nutrition Books

Annual Review of Physiology. Vol. VII. Edited by James Murray Luck and Victor E. Hall. American Physiological Society and Annual Reviews, Inc., Stanford Univ., California. 1945. pp. 774.

New Steps in Public Health. Twenty-Second Annual Conference of the Milbank Memorial Fund, April 12–13, 1944. New York. pp. 148.

The Estimation of Vitamin A. N. T. Gridgeman. Lever Brothers & Unilever Ltd., London, E. C. 4. 1944. pp. 74.

Hospital Diets. War Department Technical Manual (TM 8-500). U. S. Government Printing Office, Washington, D. C. 1945. pp. 132.

Report of the Administrator of Agricultural Research. U. S. Department of Agriculture, Agricultural Research Administration, Washington, D. C. 1944. pp. 234.

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2. The development of an educational program to facilitate the widest possible usage of what is known in the science of nutrition.

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